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Acrocallosal Syndrome in an Algerian Boy Born to Consanguineous Parents: Review of the Literature and Further Delineation of the Syndrome

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We present a 17-month-old boy with the acrocallosal syndrome. He was born to consanguineous parents. Abnormal findings included agenesis of the corpus callosum, a ventricular septal defect (VSD), postaxial polydactyly of fingers, cleft soft palate, intestinal malrotation, large anterior fontanelle, prominent forehead, hypertelorism, epicanthic folds, short nose and mandible and preauricular skin tags, mixed hearing loss, laryngomalacia, and growth and severe motor and mental retardation. A review of previous reports on the acrocallosal syndrome shows considerable clinical variability; minimal diagnostic criteria are proposed. A developmental field defect with disturbance of midline development is suggested. Am. J. Med. Genet. 69:17–22, 1997.

KEY WORDS: acrocallosal syndrome; agenesis of corpus callosum; polydactyly; developmental field defect

INTRODUCTION

In 1979, Schinzel described a 3-year-old boy with a syndrome of absence of the corpus callosum (CC), macrocephaly, hypertelorism, small nose, bilateral inguinal hernias, tetramelic postaxial polydactyly, duplication with syndactyly of the big toes, marked growth retardation, recurrent infections, cyanotic spells, seizures, and gross motor and mental retardation [Schinzel, 1979]. One year later, he reported a second case [Schinzel and Schmid, 1980] and delineated the "acrocallosal syndrome" (ACS): both patients had severe mental retardation, absence of the CC, unusual facial appearance, macrocephaly, duplication of hallucal phalanges, postaxial hexadactyly of finger phalanges, and partial syndactyly of toes 2–3. Since these first descriptions, several further patients with ACS have been reported, and considerable clinical variablity of ACS and several additional findings have been shown (Table I).

In this paper we describe an Algerian boy born to consanguineous parents with the pattern of multiple congenital anomalies characteristic for ACS.

CLINICAL REPORT

The propositus, a boy, was the sixth child of a normal 36-year-old mother and 56-year-old father who are first cousins. The mother had previously had one miscarriage and 5 healthy children, 3 boys and 2 girls. Maternal and paternal grandparents were also first cousins. There is one maternal cousin with cleft lip and one paternal cousin who died neonatally. No other birth defects are known in the family.

Delivery occurred at 40 weeks of a normal pregnancy. Birth weight was 2,850 g, length 52 cm, and occipitofrontal head circumference (OFC) 31 cm. Apgar scores were 4, 8, and 9 after 1, 3, and 5 minutes, respectively. The following anomalies were noted: laryngomalacia (stridor), cleft soft palate, bilateral metatarsus adductus, a 2/6 heart murmur (VSD, right ventricular hypertrophy), bilateral preauricular tags, and bilateral postaxial polydactyly of fingers (rudimentary extra digits). When the subject was 3 months old, the preauricular tags, sixth fingers, and bilateral inguinal hernias were operated on. The boy was transferred to our hospital at the age of 6½ months for evaluation of feeding difficulties and failure to thrive. His weight, length, and OFC were 5,200 g (<3rd centile), 64 cm (3rd to 10th centile), and 41 cm (<3rd centile), respectively. The following abnormal findings were noted (Fig. 1): large anterior fontanelle, prominent forehead, hypertelorism, epicanthal folds, short nose with anteverted nostrils, high arched palate with cleft soft palate, small mandible, dysplastic, posteriorly rotated ears, bilateral narrow external auditory canals, widely spaced nipples, a right single palmar crease, surgical scars

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TABLE I. ACS Characteristics

	34 cases[a] (%)	Our case
Sex	M 21/F 13	M
Consanguinity	24 −/10 +	+
Total or partial agenesis of the corpus callosum	34/34 (100)	+
Mental retardation	29/31 (93) (24 specified as severe)	Severe
Hypotonia	25/28 (89)	+
Polydactyly		
Postaxial		
Hand/foot	21/34 (62)	
Hand	19/34 (56)	+
Foot	12/34 (35)	
Preaxial		
Hand/foot	25/34 (73)	−
Hand	6/34 (18)	
Foot	21/34 (62)	
Craniofacial dysmorphism		
Prominent forehead	29/32 (91)	+
Hypertelorism and/or broad nasal bridge	31/33 (94)	+
Short nose with anteverted nostrils[b]	23/29 (79)	+
Large anterior fontanel	21/22 (95)	+
Highly arched/cleft palate	21/27 (78)	+
Abnormal ears (low set/posteriorly rotated)	23/27 (85)	+
Epicanthal folds	18/20 (90)	+
Inguinal hernia	11/23 (48)	+
Umbilical hernia	5/30 (17)	−
Seizures	12/33 (36)	−
Hypogenitalism/hypospadias (males)	13/21 (62)	−
Tapered fingers	11/12 (92)	+
Congenital heart defect	6/27 (22)	+

[a] Gelman-Kohan: patients 2 and 3 with ACS.
[b] Abnormally shaped and broad nose with a median groove in three additional cases (Sueldo, Guion, Toriello).

from amputation of the rudimentary extra digits at the lateral sides of the fifth fingers at the level of the first phalanges bilaterally, tapering fingers, bilateral metatarsus adductus. He showed generalized muscular hypotonia (was unable to support his head) with substantial psychomotor retardation (developmental level at ± 2½ months).

Ophthalmologic examination was suggestive of right microphthalmia and bilateral microcornea. Auditory brainstem evoked responses demonstrated mixed (conductive and sensorineural) hearing loss (80–85 dB and 65–70 dB on the right and left side, respectively, after treatment of otitis). Bronchoscopy showed an anteriorly displaced glottis and laryngomalacia. A brain magnetic resonance showed agenesis of the corpus callosum (Fig. 2). Radiographic findings included tapering distal phalanges of all digits, relatively broad first metacarpals and proximal phalanges bilaterally, an increased distance between toes 1 and 2, broad halluces, generalised osteopenia, and pronounced dorsal kyphosis. An operation intervention for intestinal malrotation was performed.

Failure to thrive persisted. At 17 months, weight was 7,190 g (<3rd centile), length 74 cm (<3rd centile), and OFC 45 cm (<3rd centile) (Fig. 3). His anterior fontanelle was still very large (6.5 cm on 2 cm); he had four normal teeth, and the fourth left finger showed hyperlaxity of the proximal interphalangeal joint. He was unable to hold his head or sit alone, had stereotypic and dysharmonic movements (developmental age of nearly 3 months), and was still tube-fed. He has developed bilateral myopia (of −6.5 and −5.5 at the right and left eye, respectively). Cardiac reevaluation disclosed only a minor right bundle branch block (VSD spontaneously closed). Radiographic findings included hypoplastic mandible with an obtuse angle, hypoplastic midface, bilateral pseudoepiphyses at the bases of the second metacarpals with delayed bone age, dense mastoids and maxillary sinuses, and a misshaped sella turcica (tubercle of the sella is absent). He had frequent respiratory infections and had been hospitalized nearly constantly since birth. G-banded prometaphase chromosome analysis from peripheral lymphocytes and a G-banded karyotype from skin fibroblasts (50 mitoses) were normal.

Results of renal ultrasonography, eye fundus, slit lamp examination, flash evoked visual potentials, upper limb somatosensory evoked potentials, electroencephalography (EEG), and metabolic screen were normal.

DISCUSSION

The pattern of multiple congenital abnormalities, including agenesis of the corpus callosum (CC), postaxial polydactyly of the hands, large anterior fontanelle, prominent forehead, hypertelorism, epicanthal folds, short nose with anteverted nostrils, and severe mental retardation found in the patient of this report is com-

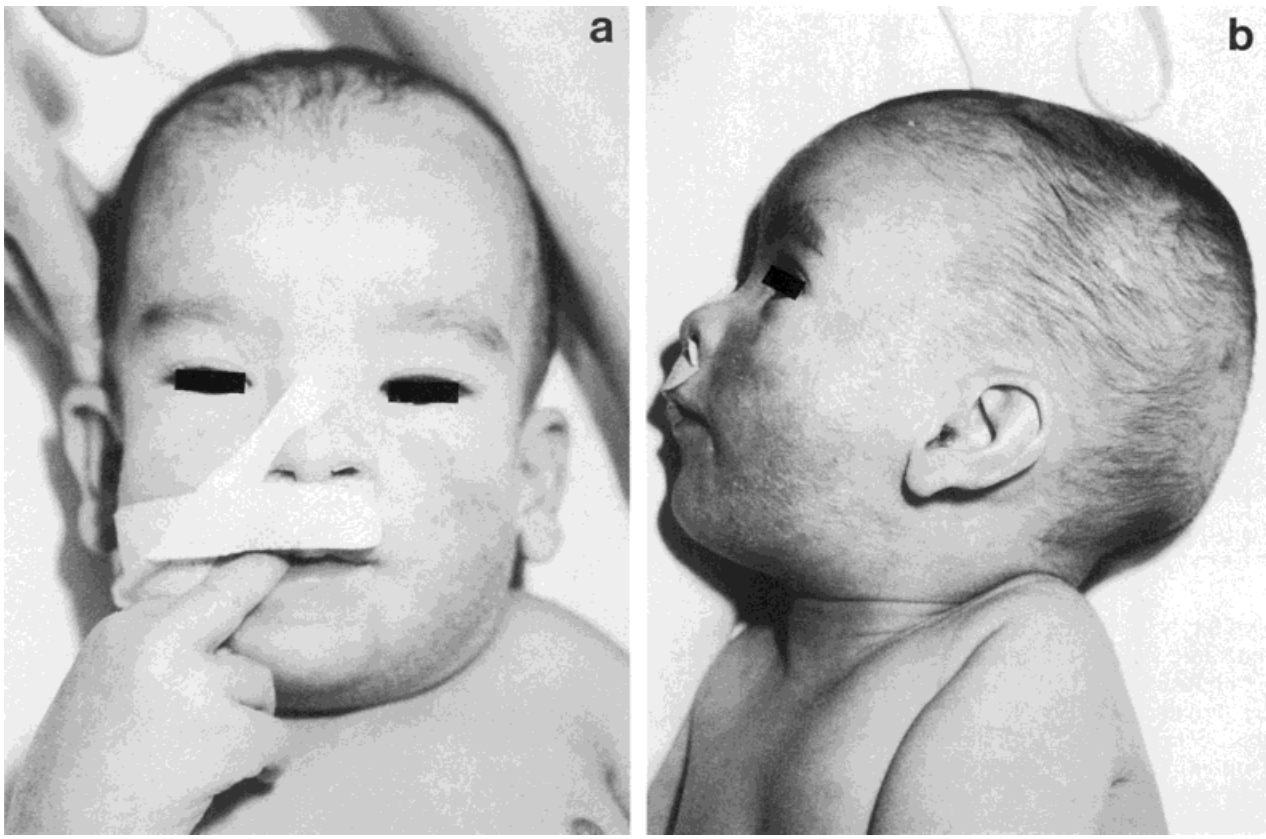

Fig. 1. **a,b:** Clinical appearance of the index case at the age of $6^1/_2$ months.

patible with the diagnosis of acrocallosal syndrome (Table I). Further abnormal findings of our patient can also be found in other reports of ACS (Table II). Our case does not present macrocephaly, a frequent finding in ACS, but this finding can be absent, especially in younger children [Toriello et al., 1986; Turolla et al., 1990; Lurie et al.,1994] and might appear later on [Schinzel, 1980; Christianson et al., 1994]. Neither intestinal malrotation nor an anteriorly displaced glottis have yet been described. However, in the patient of Schinzel [1979], bronchoscopy disclosed an anterior subglottis bulge.

There are many similarities between our patient and the one reported by Buntinx and Majewski [1990] as "new syndrome?". Common characteristics are agenesis of the CC, postaxial polydactyly of hands, facial appearance (prominent forehead, large anterior fontanelle, epicanthus, short nose with anteverted nostrils, apparently low-set posteriorly angulated ears, highly arched palate, very narrow external meati), prominent heels, truncal hypotonia, failure to thrive, bilateral conductive and sensorineural hearing loss, and severe development delay. We suggest that this case could also be classified as ACS, since many of the findings fit this diagnosis. However, ACS is not mentioned by these authors as a possible differential diagnosis. There is indeed a difficulty in diagnosing ACS, since minimal diagnostic criteria have not yet been established.

As with most malformation syndromes, the delineation of ACS has changed with time, as it became evident that the clinical spectrum was wider and more variable than the first reports had suggested. Preaxial

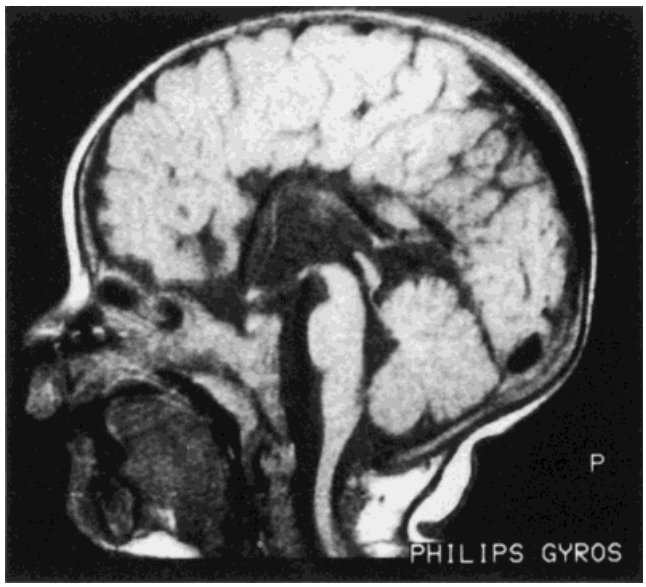

Fig. 2. Agenesis of the corpus callosum (MRI).

Fig. 3. Clinical appearance of the patient at the age of 17 months (craniofacial anomalies, tapering fingers).

polydactyly, first considered a consistent finding in this syndrome, is not always present: actually, of the 34 reported patients, only 10 have postaxial (and not preaxial!) polydactyly [Sanchis et al., 1985; Philip et al., 1988; Schinzel, 1988; Temtamy and Meguid, 1989; Turolla et al., 1990; Yüksel et al., 1990; Gelman-Kohan et al., 1991; Christianson et al., 1994], and there is even one case [Guion-Almeida and Richieri-Costa, 1992] with neither pre- nor postaxial polydactyly clinically (but the radiographic findings do show a bifid distal phalanx at right and duplication at left). Various cardiac defects have been described: atrial septal defect [Schinzel, 1982; Christianson et al., 1994], dysplastic pulmonary valve [Moeschler et al., 1989], dextroposition of the aorta with an ostium secundum [Philip et al., 1988], tetralogy of Fallot [Casamassima et al., 1989], unusual configuration and position of both ventricles [Schinzel, 1979], VSD [Christianson et al., 1994].

A review of the clinical findings of the reported cases with ACS (Table I) allows us to define minimal diagnostic criteria:

1. Total or partial absence of the CC
2. Minor craniofacial anomalies (prominent forehead, hypertelorism, short nose with anteverted nostrils, large anterior fontanelle)
3. Moderate to severe psychomotor retardation (with hypotonia)
4. Polydactyly

The presence of 3 of the 4 criteria together with other associated findings could lead one to suspect the diagnosis of ACS.

To be excluded are chromosome abnormalities [reviewed in Temtamy, 1989] and a few other malformation syndromes. The similarity (digital changes and minor anomalies) with the Greig cephalopolysyndactyly syndrome (CGPS) has been discussed [Schinzel 1982; Legius et al., 1985; Hendriks et al., 1990], although agenesis of the CC and mental retardation are rare in the latter. Brueton and colleagues [1992] provided evi-

TABLE II. Other Anomalies Present in Our Patient, Reported in Other Cases With ACS

Mild conductive hearing loss	Hendriks et al., 1990
Bilateral sensorineural hearing loss	Cataltepe and Tuncbilek, 1992
Narrow external meati of the ears	Moeschler et al., 1989
Preauricular tags	Schinzel and Kaufmann, 1986
	Sanchis et al., 1985
	Wendisch et al., 1990
Simian crease	Turolla et al., 1990
	Moeschler et al., 1989
	Guion-Almeida and Richieri-Costa, 1992
	Pfeiffer et al., 1992
A wide gap between first and second toes	Turolla et al., 1990
Hyperextensibility of one finger	Lungarotti et al., 1991
Metatarsus adductus	Pfeiffer et al., 1992
A rudimentary postaxial polydactyly of the hands	Schinzel, 1979, 1980
	Nelson and Thomson, 1982
	Legius et al., 1985
	Toriello et al., 1986
	Salgado et al., 1989
	Yüksel et al., 1990
	Lungarotti et al., 1991
	Gelman-Kohan et al., 1991
	Wendisch et al., 1990
Frequent respiratory infections	Schinzel, 1979
	Pfeiffer et al., 1992
	Nelson and Thomson, 1982
	Yüksel et al., 1990
Failure to thrive	Schinzel, 1979
	Schinzel and Schmid, 1980
	Nelson and Thomson, 1982
	Hendriks et al., 1990
	Christianson et al., 1994

dence that the ACS and GCPS do not result from allelic mutations nor do they represent contiguous deletions of different size involving the same segment on the short arm of chromosome 7.

Differential diagnoses in our patient may include the cerebrooculofacioskeletal, Aicardi, Neu-Laxova, OFD II, pseudotrisomy 13, Toriello-Carey [1988], otopalatodigital II [Holder and Winter, 1993], and Da Silva [1988] syndromes. These syndromes seem to be excluded, or at least much less likely, by the combination of findings present in our male patient.

The diagnosis of ACS may sometimes be very difficult and subject to debate: the boy reported by Toriello [1986] was suspected by Schinzel [1987] to have ACS; a suggestion accepted by Toriello herself [1987] but not by others [Gorlin, 1990]. The Toriello syndrome [1986] is also classified as a subtype of acromelic frontonasal "dysplasia" [Verloes et al., 1992; Verloes, 1994]. In a patient with agenesis of the CC, postaxial polydactyly of fingers, pre- and/or postaxial polydactyly of toes, micrognathia, cleft lip/palate and facial anomalies, but no hydrocephalus [Anyane-Yeboa et al., 1987; Bachman et al., 1990], the hydrolethalus syndrome might also be difficult to exclude in differential diagnosis.

It was first suggested that the inheritance of ACS could be autosomal dominant, since the first published cases all occurred sporadically. Recently, ACS has been classified as being autosomal recessive [MIM 200990] on the basis of two pairs of affected sibs with normal parents [Schinzel, 1982, 1986; Christianson et al., 1994], two affected first cousins [Schinzel, 1988], six unrelated children of consanguineous parents [Philip et al., 1988; Salgado et al., 1989; Temtamy and Meguid, 1989; Yüksel et al., 1990; Cataltepe and Tuncbilek, 1992] and a report describing a large inbred kindred with recurrent ACS [Gelman-Kohan et al., 1991]. Only three families with at least two affected sibs with ACS have been reported [Schinzel, 1986; Gelman-Kohan et al., 1991; Christianson et al., 1994].

Pfeiffer and coworkers [1992] described a case with findings compatible with ACS who had an unbalanced rearrangement of the short arm of chromosome 12 interpreted cytogenetically as an inverted tandem duplication of 12p11.2-p13.3. The authors argued in favour of their interpretation that the patient's clinical findings also resembled those of patients with trisomy and tetrasomy 12p. However, the origin of the additional material on 12p was not determined with molecular methods [Docherty and Seller, 1993].

ACS could be a developmental field defect [Toriello et al., 1986]: a primary field defect with predominantly midline formation defect as defined by Opitz [1982, 1994]. Reviewing the findings described in reported ACS patients, we ascertain a large number of midline anomalies. These include, in addition to the manifestations outlined above, one case with an anteriorly placed anus [Philip et al., 1988], one with a decreased tracheal caliber on bronchoscopy [Moeschler et al., 1988], and intestinal malrotation in our case.

Therefore we could suggest that the genetic defect causing this syndrome probably exerts its major influence on various midline developmental processes early in embryogenesis, causing CNS defects (agenesis of the CC, Dandy-Walker malformation, anencephaly), cleft lip/palate, congenital heart defect, hypospadias and other defects. Intra- or intergenic modifying factors probably play a role in the variability of the manifestations [Gelman-Kohan et al., 1991].

Clinical variability is clearly demonstrated in patients with ACS; the clinical spectrum of ACS may be still larger than previously described (midline defects), including the suggestion that anencephaly could be an extreme manifestation of ACS-related brain defects [Gelman-Kohan et al., 1991; Cataltepe and Tuncbilek, 1992; Lurie et al., 1994] and that less typical cases may not be diagnosed.

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